Remarks

The foregoing amendments are of formal nature and serve to correct obvious typographical errors. The amendment do not add new matter.

The Office Action

Prior to entry of the foregoing amendments, claims 27-52 were pending in the application. Claims 47 to 51 were withdrawn from consideration and are now canceled. Claims 27-33, 35, 36, 38-46, and 52 were rejected on various grounds, and claims 24 and 37 were objected to. All rejections and objections are respectfully traversed.

Election/Restriction

Applicants note the finality of the restriction requirement, and have canceled non-elected claims 47-51.

Claim Rejections - 35 U.S.C. § 112

(a) *Written Description*

Claims 27-33, 35, 36 and 52 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description.

The Examiner objects that the broader claims do not meet the written description requirement, on the grounds

(1) that the description and claims do not indicate the distinguishing attributes shared by members of the genus, and

(2) that the general knowledge and level of skill in the art does not supplement this omission.

Applicants submit that the Examiner's position is unjustified on both grounds.

Concerning the first ground, it is precisely the formula provided in the claims that provides the distinguishing attributes of the genus. This is illustrated by the teaching of Example 8 (pages 32-36 of the substitute specification).

In the following discussion, reference will be made particularly to the amino acid sequence of claim 27:

R_1-X-F-X-R_2-R_3-W-X-X-R_4 (SEQ ID NO: 4)

The sequences set out on page 35, lines 7-14 are those of the wild-type dm2 binding site on human p53 (SEQ ID NO:1), the amino acid sequences displayed by several phages that bind to human DM2 (SEQ ID NOS: 6, 63, 64, 65, 8 and 66) and a consensus sequence derived from the phage sequences (SEQ ID NO: 3).

The amino acid residues at certain positions in the phage sequences are invariant compared to the wild-type sequence, at others there is a consensus despite some variation and at still others there is no consensus at all. As will become clear, an analysis of these similarities and differences provides support for the formula of SEQ ID NO: 4.

Most notably, amino acids F and W (shown in bold on page 35) are invariant among the phage sequences, at positions corresponding to positions 3 and 7 in SEQ ID NO: 4. These positions are defined in SEQ ID NO: 4 as the amino acids F and W, respectively.

By contrast, at the position corresponding to position 2 in SEQ ID NO: 4, the phages do not display an invariant or even a consensus residue. The same applies to positions 4, 8 and 9. For each of these positions, no more than two sequences among the phage sequences and the wild-type sequence show the same residue. These positions are defined as "any natural amino acid" in claim 27.

Lastly, at positions corresponding to the remaining positions in SEQ ID NO: 4 (positions 1, 5, 6 and 10), the phages show a consensus residue (of P, D, Y and L, respectively). However, they also show that certain other amino acids can be present at these positions, while still permitting binding to HDM2. These positions are defined as a limited number of possible amino acids in claim 27.

Moreover, the variation at positions 1, 5, 6 and 10 is independent: in the phage represented by SEQ ID NO: 63, the residues at positions 1 and 10 differ from the consensus; in the phage represented by SEQ ID NO: 64, the residues at positions 5 and 10 differ from the consensus; in the phage represented by SEQ ID NO: 65, the residue at position 6 differs from the consensus; in the phage represented by SEQ ID NO: 8, the residue at position 1 differs from the consensus; and in the phage represented by SEQ ID NO: 66, the residues at positions 4 and 5 differ from the consensus.

Accordingly, the formula of claim 27 represents a reasonable generalization of the specific phage sequences presented on page 35. Thus, the generic formula does indeed contain the structural features (i.e. the invariant amino acids F and W and the limited range of amino acids at positions 1, 5, 6 and 10) that distinguish compounds within the genus.

Turning now to the second ground, the paragraph bridging pages 1 and 2 of the application points out that it was known that "peptide fragments pf p53 which include the amino acid motif FxxLW ... would be particularly suitable for interfering with the binding between p53 and mdm2". This finding is elaborated further in WO96/02642 (IDS Reference # AH), which was published before the filing date of the application. The first- and last-named authors of the Picksley et al. paper to which the application refers are the inventors of WO96/02642.

Three US patents equivalent to WO96/02642 have been granted: US 6,153,391; US 5,770,377 and US 5,702,908, copies of which are submitted with the attached Supplemental Information Disclosure Statement. We refer particularly to US 6,153,391, Claim 1 of which (when read in combination with claim 10) recites:

> "A method for interfering with the binding of p53 to [MDM2] or a fragment thereof that binds to p53, said method comprising:
>
> contacting said p53 and [MDM2] or fragment thereof with a compound comprising ... (b) a peptide analogue of the peptide fragment of (a) which comprises the sequence FxxLW ...
>
> wherein ... (b) ... binds to said [MDM2] or fragment thereof and thereby interferes with its binding to said p53."

(a) recites a fragment of p53 comprising the FxxLW motif.

As the Examiner will appreciate, in this motif, and in peptides bearing the motif, the only specified invariant residues are F, L and W.

Thus, it has been recognized previously by the USPTO that this motif represents an acceptable generic formula to define peptides that interfere with the binding of MDM2 to p53.

As previously explained, the present invention differs from these prior art disclosures by virtue of the definition of R_3 in SEQ ID NO: 4. In the prior art, wild-type p53 sequences, the residue at this position is L; by contrast, in the compounds of the invention, R_3 is defined as H, F or Y.

These prior art disclosures provide support for the inclusion of variable residues in the generic formula of SEQ ID NO: 4, and it is noteworthy that the prior art motif only defines 3 residues. By contrast, SEQ ID NO: 4 defines no fewer than 6 residues, albeit some being defined as one of a few or several amino acids. Taken as a whole, however, the formula represented by SEQ ID NO: 4 defines a significantly narrower (and of course distinct) genus than that recognized as patentable (and therefore meeting the written description requirement) in US 6,153,391.

Accordingly, the prior art also reasonably conveys to one skilled in the art that the inventors were in possession of a genus of compounds, as defined in claim 27, that inhibit the binding of DM2 to p53, and the present rejection should be withdrawn.

(b) *Enablement*

Claims 27-33, 35, 36, 38-46 and 52 have been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Examiner has acknowledged, however, that the disclosure was enabling for compositions comprising SEQ ID NOs: 6-8 and 12-14, methods for inhibiting MDM2 binding to p53 in vitro comprising SEQ ID NOs: 6-8 and 12-14, and purification of SEQ ID NOs: 6-8 and 12-14.

There appear to be two ground to the rejection. Firstly that the broader claims are not enabled generally and secondly that the narrower claims (whilst being enabled generally) are not enabled for *in vivo* administration.

In relation to the first ground, the Examiner refers to Parsons et al. as indicative of the state of the art. As the Examiner points out, Parsons et al. states that "[T]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study."

This statement is, however, inapplicable to the present case, for the simple reason that the present application builds on and further develops earlier experimental work. That experimental work, acknowledged in the application and described above with particular reference to US 6,153,391, shows that the significance of particular amino acids from p53 in the binding of DM2 was already significantly understood. As mentioned above, the US PTO has already recognized that the motif FxxLW represents an acceptable generic formula to define peptides that interfere with the binding of MDM2 to p53.

The objection is therefore based on a mischaracterization of the prior art.

Moreover, apart from defining the generic formula in claim 27, the application provides ample guidance as to preferred amino acids for the variant positions. Page 3, lines 7-10 indicate that R_2 is preferably D, R_3 is preferably Y and R_4 is preferably L. Page 4, lines 21-24 indicate that X_1 is preferably R, N, A, T or V, X_2 is preferably M, I, T, R, A or S, X_3 is preferably E, T, A, F or S and X_4 is preferably G, E, T, A or D.

Accordingly, the application provides ample guidance to the skilled person to work the invention across the scope of SEQ ID NO:4, as recited in claim 27.

In relation to the second ground, we point out that none of the claims requires *in vivo* administration. The pending independent claims are directed to compounds per se (claim 27), a method of inhibiting binding of a DM2 protein to a p53 protein (claim 41) and a purification method (claim 43). None of the independent or dependent claims makes any reference to *in vivo* administration.

Furthermore, when the Examiner concludes that a claimed invention is not enabled, the initial burden is on the Examiner to provide a reasonable basis to support this conclusion. In the present case, the Examiner provided no specific reasoning why the disclosure provided in the specification, in view of general knowledge in the art at the priority date, would not enable one

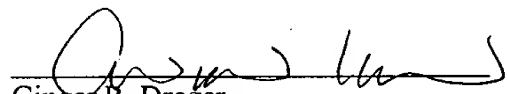
skilled in the art to practice the methods claimed in claims 41 and 42 *in vivo*. Since a *prima facie* case of lack of enablement has not been established, the burden to rebut this rejection has not shifted to Applicants, and the rejection on this ground should be withdrawn.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39749-0002APC). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Dated: November 20, 2003



Ginger R. Dreger
Reg. No. 33,055

HELLER EHRMAN WHITE & McAULIFFE, LLP
Customer No. 25213
275 Middlefield Road
Menlo Park, CA 94025
Telephone: 650/324-7000
Facsimile: 650/324-0638